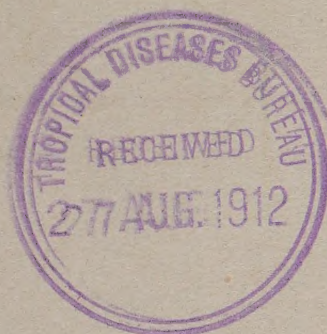


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Studies of Malaria in Panama. II. Treatment of Blackwater Fever

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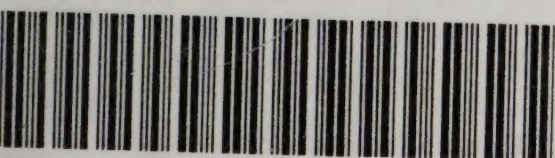
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ERYTHROLYTIC HEMOGLOBINURIA

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STUDIES OF MALARIA IN PANAMA. II. TREATMENT OF BLACKWATER FEVER

PERNICIOUS MALARIA WITH HEMOGLOBINURIA AND ERYTHROLYTIC HEMOGLOBINURIA*

WALTER BREM, M.D.

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"Blackwater fever" is a term commonly used to designate fever with hemoglobinuria, associated more or less definitely with malaria. It embraces, I believe, two types of hemoglobinuria, which should be clearly differentiated for purposes of treatment and of study. The first type is associated with enormous numbers of malarial organisms, and, like the hemoglobinuria of piroplasmiasis, its intensity is in direct relation to the severity of the infection. The mechanism of its production is, I am led to believe, the immediate destruction of erythrocytes by segmenting parasites, and differs from the mechanism of the second type, which is due, it is generally conceded, to the solution of erythrocytes by an unknown hemolysin (erythrolysis). I venture to propose, therefore, that the terms "blackwater fever," "malarial hemoglobinuria," "hemoglobinuric fever," etc., be abandoned as leading to confusion and possibly to grave errors in treatment, and that the two types of hemoglobinuria be described under a differential nomenclature.

Type 1.—Pernicious malarial fever with hemoglobinuria. The etiology is known and it is better that the condition or symptom of hemoglobinuria should not receive a more prominent place in the diagnosis.

Type 2.—Erythrolytic hemoglobinuria. Our knowledge of the etiology of this type is incomplete, and until an etiologic terminology can be rationally applied it would seem best to use one based on the mechanism of production, and on the most prominent feature of the symptom-complex.

If I may be permitted to do so, I shall employ this nomenclature.

PERNICIOUS MALARIAL FEVER WITH HEMOGLOBINURIA

A typical example of this type is presented in the case reports (Case 1, Chart 1). The hemoglobinuria was anticipated from the examination of blood about thirty-four hours before it appeared; 15.6 per cent. of red blood corpuscles in the peripheral blood were infected; the urine had the characteristic appearance of "blackwater."

* Read at the seventh annual meeting of the American Society of Tropical Medicine, St. Louis, June 11, 1910.

Since my attention was drawn to the separation of this type of hemoglobinuria, eight patients with pernicious malaria have been admitted to the hospital, and in the urine of all we were able to demonstrate the presence of hemoglobin; in the last six the blood examination led us to suspect its imminence, and to foresee approximately the time of its onset.

The hemoglobinuria varies in degree from traces of hemoglobin in the sediment discernible only by special tests to the intensity of "blackwater." Two of the eight patients mentioned voided typical "blackwater" urine;

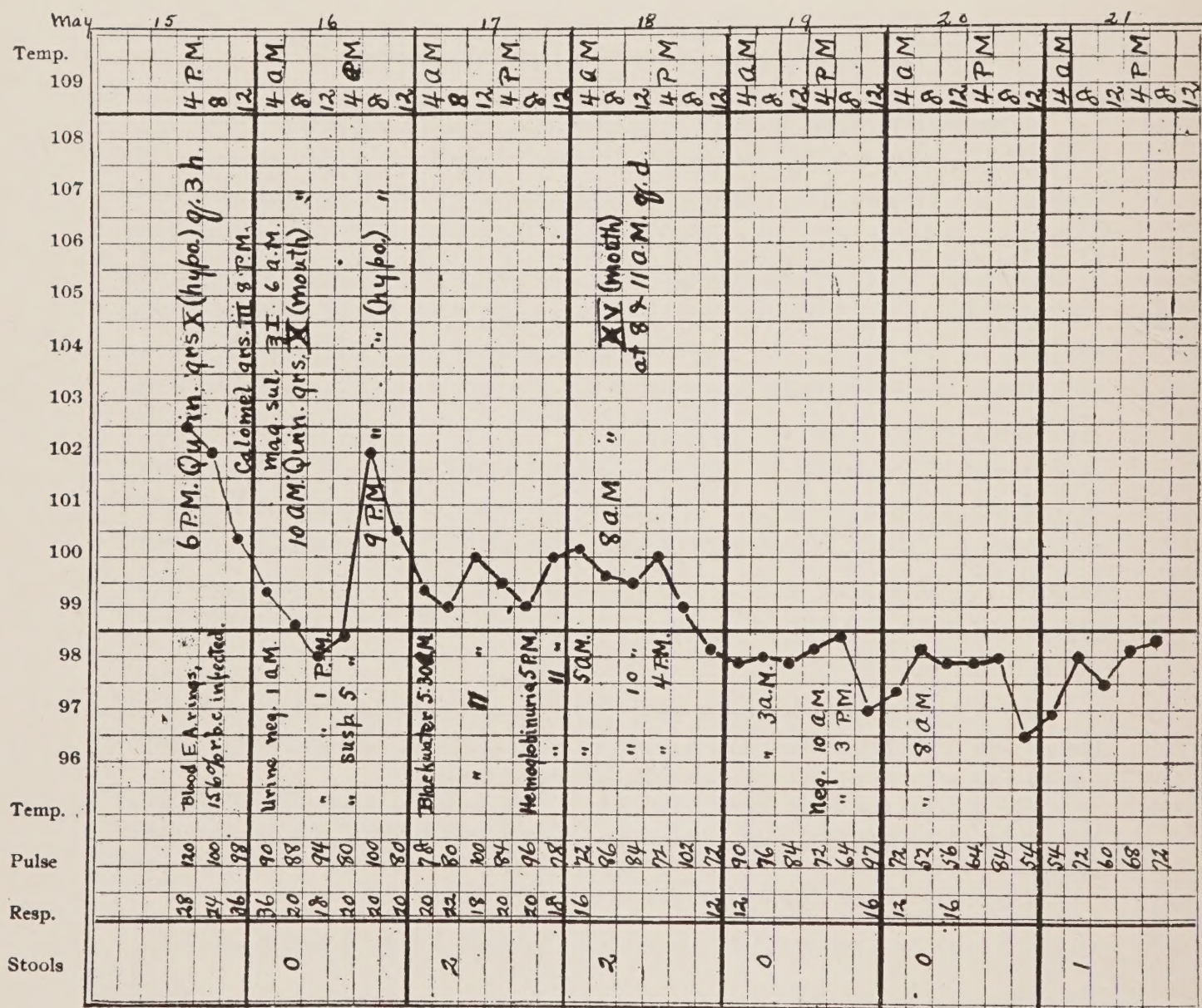


Chart 1.—Showing conditions in Case 1.—Pernicious malarial fever with hemoglobinuria.

three voided urine recognizable by the eye as probably hemoglobinous; one passed reddish-brown urine with a suggestive grayish-brown sediment; the other two, urine that, to the eye, gave no suggestion of hemoglobin, which was demonstrable only in the sediment. The guaiac and turpentine test for hemoglobin was employed. Controls were made by

testing the urine of hundreds of patients with mild or moderate malarial infections, and uniformly negative results were obtained. I feel confident, therefore, in saying that a positive reaction of the urine to the guaiac and turpentine test means the presence of hemoglobin.¹ Only a definite blue color was considered as indicating a positive reaction.

It is my belief at present that future examinations will demonstrate hemoglobinuria at some time during the course of every pernicious malarial infection. In some of the cases an examination of each specimen voided must be made, the urine must be sedimented, preferably in a conical glass, and the sediment used in the test for hemoglobin. If this belief proves to be well founded, the mortality of this type will be the mortality of pernicious malarial fever. Of my eight patients, one died from the malarial infection, the capillaries of his brain being stuffed with parasites; another died, after his malarial infection was controlled, from a subsequent infection with an organism (isolated at autopsy from the spleen) apparently belonging to the typhoid-colon group, but possessing atypical fermenting properties (no malarial parasites were found in smears from the spleen, bone-marrow and brain); the other six made rapid recoveries. I have been able to recall four other cases and to find records of two more. One of the four was a fatal case seen in Baltimore in Osler's wards in the Johns Hopkins Hospital and mentioned by me in a former report.² Five of these six patients died. This mortality is very high, because the diagnosis was made from the gross appearance of the urine, and hemoglobinous urine of blackwater intensity occurs only in the most severe infections. Among twenty deaths that I have seen associated with blackwater, five of them, or 25 per cent., were due to pernicious malarial infections. It would seem, therefore, that a considerable percentage of deaths, heretofore reported as due to blackwater fever, were really due to pernicious malarial fever with hemoglobinuria, which fact has an important bearing on comparative mortality statistics under differ-

1. The following modification of the guaiac-turpentine test has been developed in the clinical laboratory of Coloma Hospital for the examination of urine: Place 3 to 5 c.c. of urine containing sediment in a test-tube, add a few drops of glacial acetic acid; after a moment add 1 to 2 c.c. of ether and agitate gently, then a pinch of powdered guaiac resin, and lastly 10 to 20 drops of old turpentine. A pale blue to a blue-black color indicates a positive reaction, which may take a few moments to develop. If the ether does not separate well, a few drops of alcohol will facilitate the separation. The blue color may be brought out and the test rendered more delicate in doubtful cases by the following procedure: To the ether-turpentine mixture add chloroform drop by drop until all of the resultant mixture, except a thin layer, has been sunk to the bottom. To the thin layer remaining at the top, add carefully two or three drops of alcohol, then a few drops more of old turpentine. If inadvertently all of the ether-turpentine mixture has been sunk by adding too much chloroform, the alcohol and turpentine may be added as before and then a few drops of the sunken mixture recovered with a small pipette and added to the top layer.

2. Brem, W.: Malarial Hemoglobinuria, Jour. Am. Med. Assn., 1906, xlvii, 1896, 1992.

ent systems of treatment. Among twelve cases of blackwater fever in Panama, reported by Whipple,³ in a pathologic study, three appear to have been of this type, and Whipple separates them from the ordinary type by designating them as “pernicious malaria and blackwater fever.” Whipple made the important observation that the pathology of these cases, and, also, of pernicious malaria without apparent hemoglobimuria does not differ essentially from that of “blackwater fever.” Whipple did not observe evidence of hemoglobinuria in five other cases of pernicious malaria reported in the same study. But the detection of a mild

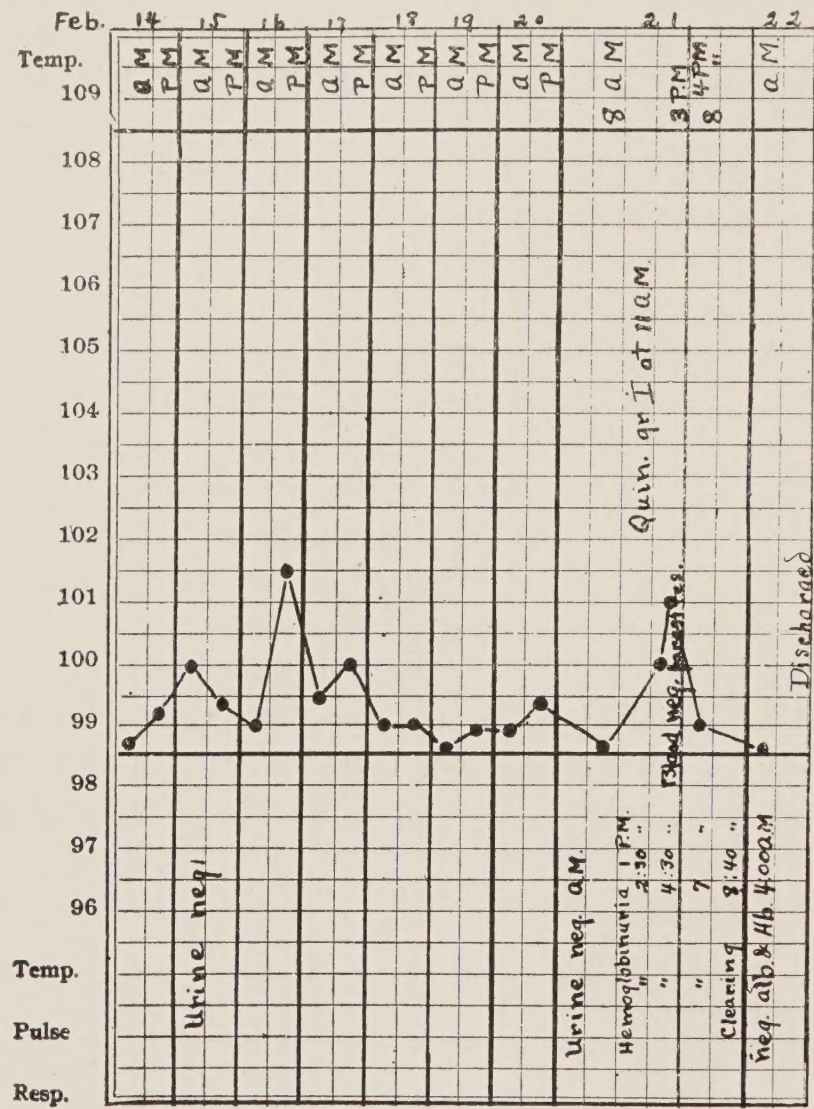


Chart 2.—No. 23,831. Patient, Frenchman, who had been on Isthmus six years, was admitted to Ancon hospital, Feb. 14, 1907. The patient had had several previous attacks of fever, “blackwater” being precipitated by quinin. The spleen was about 6 cm. below costal margin. The patient consented to take 1 grain of quinin as an experiment; blackwater followed in two hours. (Case from the clinic of Dr. A. B. Herrick, who kindly permits me to use it.)

grade of hemoglobinuria by a microscopic examination of kidneys would be a difficult or impossible task, and, as Whipple points out, the differ-

3. Whipple, G. H.: Blackwater Fever and Pernicious Malaria in Panama, Malaria, Leipsic, 1909, i, 4, 215.

ence in the pathology is one of degree and not of kind. Moreover, the hemoglobinuria of pernicious malarial fever seems to be in proportion to the absolute number of parasites, and in treated cases these are always decimated by quinin in the general circulation, while death is usually produced by those blocking the capillaries of the brain. This is well illustrated by one of Whipple's cases (No. 1431). As a rule, then, when treated patients come to autopsy, the hemoglobinuria has almost or entirely disappeared.

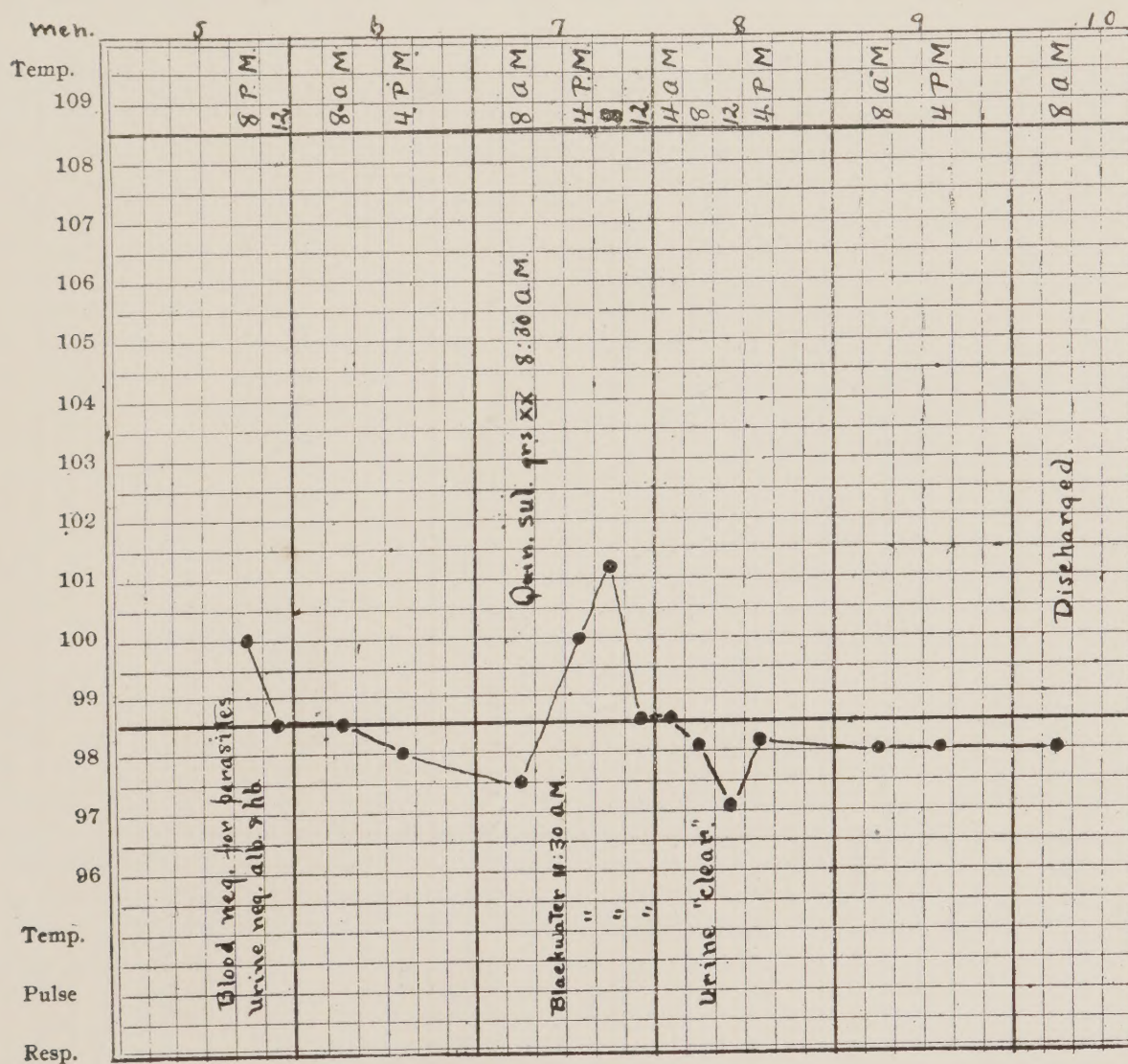


Chart 3.—No. 10,077. Patient, colored man from Antigua, W. I., who had been on the Isthmus five months, was admitted to Colon hospital, March 5, 1908. The patient passed "bloody urine" after taking quinin three weeks before admission. On the day before admission he felt sick and took 15 or 20 grains of quinin, after which he passed "bloody urine" again. After admission the urine was negative for albumin and hemoglobin. Quinin was withheld until the third day at 8:30 a. m., when 20 grains was given. "Blackwater" appeared at the third urination, two hours after quinin, and hemoglobinuria persisted until the next morning.

The differentiation of pernicious malarial fever with hemoglobinuria from erythrolytic hemoglobinuria rests chiefly on blood examinations. But occasionally parasites may not be numerous in the peripheral blood

while they may be swarming in the internal organs. In such a case, cerebral symptoms (delirium, stupor or coma), which are rare in erythrolytic hemoglobinuria, may lead one to a correct diagnosis. The importance of the differentiation from the standpoint of treatment is obvious, for whatever may be one's belief regarding the treatment of erythrolytic hemoglobinuria, there can be no question but that in the pernicious malarial type the infection overshadows the hemoglobinuric condition, and that quinin in large doses must be introduced promptly into the blood-stream. If the patient is not vomiting and the attack seems only

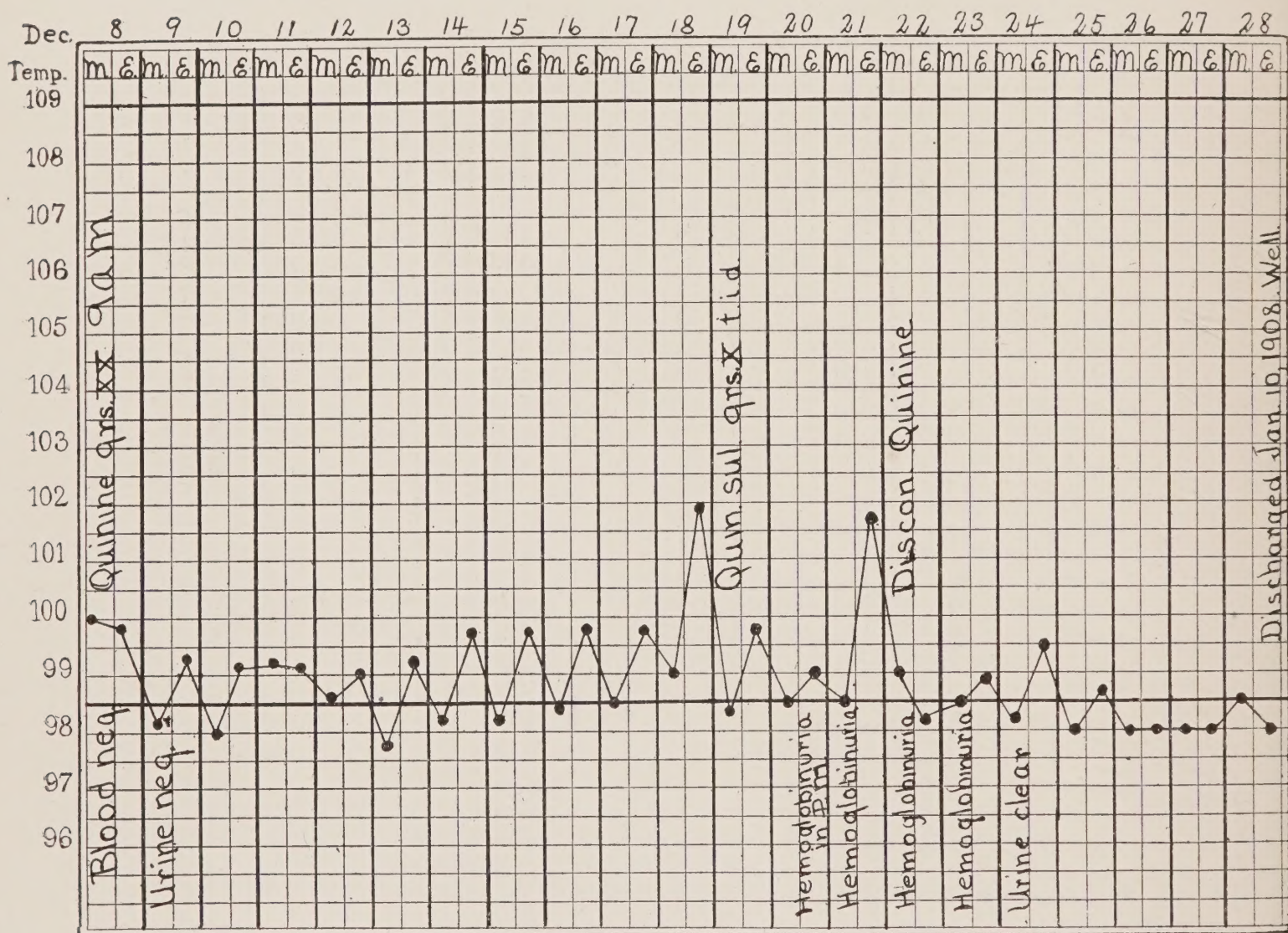
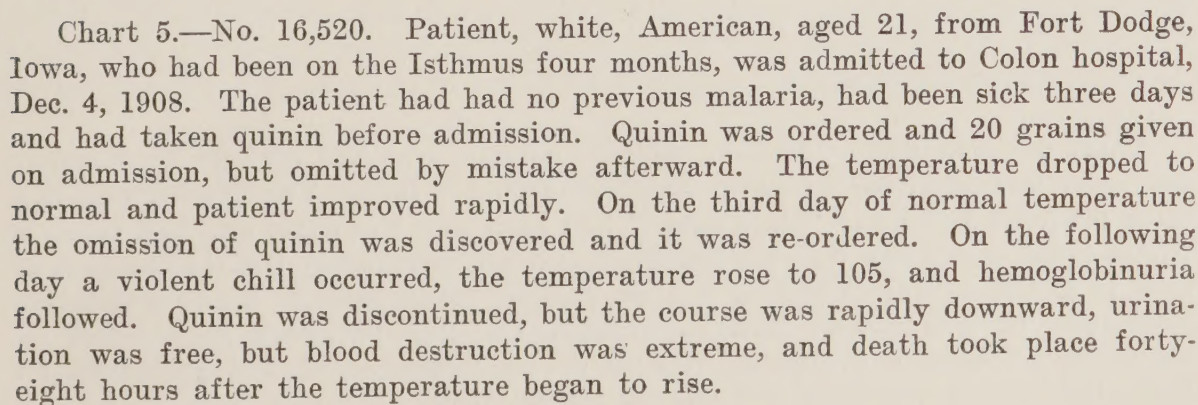


Chart 4.—No. 8,711. Patient, colored man from Jamaica, who had been in Panama two and a half years, was admitted to Colon hospital, Dec. 8, 1907. The patient had chill with blackwater Nov. 19, 1907, about nineteen days before admission. Hemoglobinuria did not follow one dose of quinin given on admission. After ten days quinin grs. x, t. i. d. was ordered, and hemoglobinuria developed the next day; it subsided when quinin was discontinued. The patient's brother was in the hospital at the same time with hemoglobinuria (Chart 15).

moderately severe, 10 grains of quinin in solution by mouth every three or four hours may be sufficient, the absorption being determined by tests for the drug in the urine. If vomiting supervenes, quinin must be



in the intracorpuseular stage of the cycle, and thus to prevent them from reaching maturity. It seems certain that a large proportion of them can be killed in this stage, and the evidence is good that many infected corpuscles can be saved. (Case 1, hemoglobin and r. b. c. records).

ERYTHROLYTIC HEMOGLOBINURIA

This type of hemoglobinuria is of course the common one and the one under special discussion in this paper. The material for my study has been collected from the records of Ancon Hospital from 1904 to

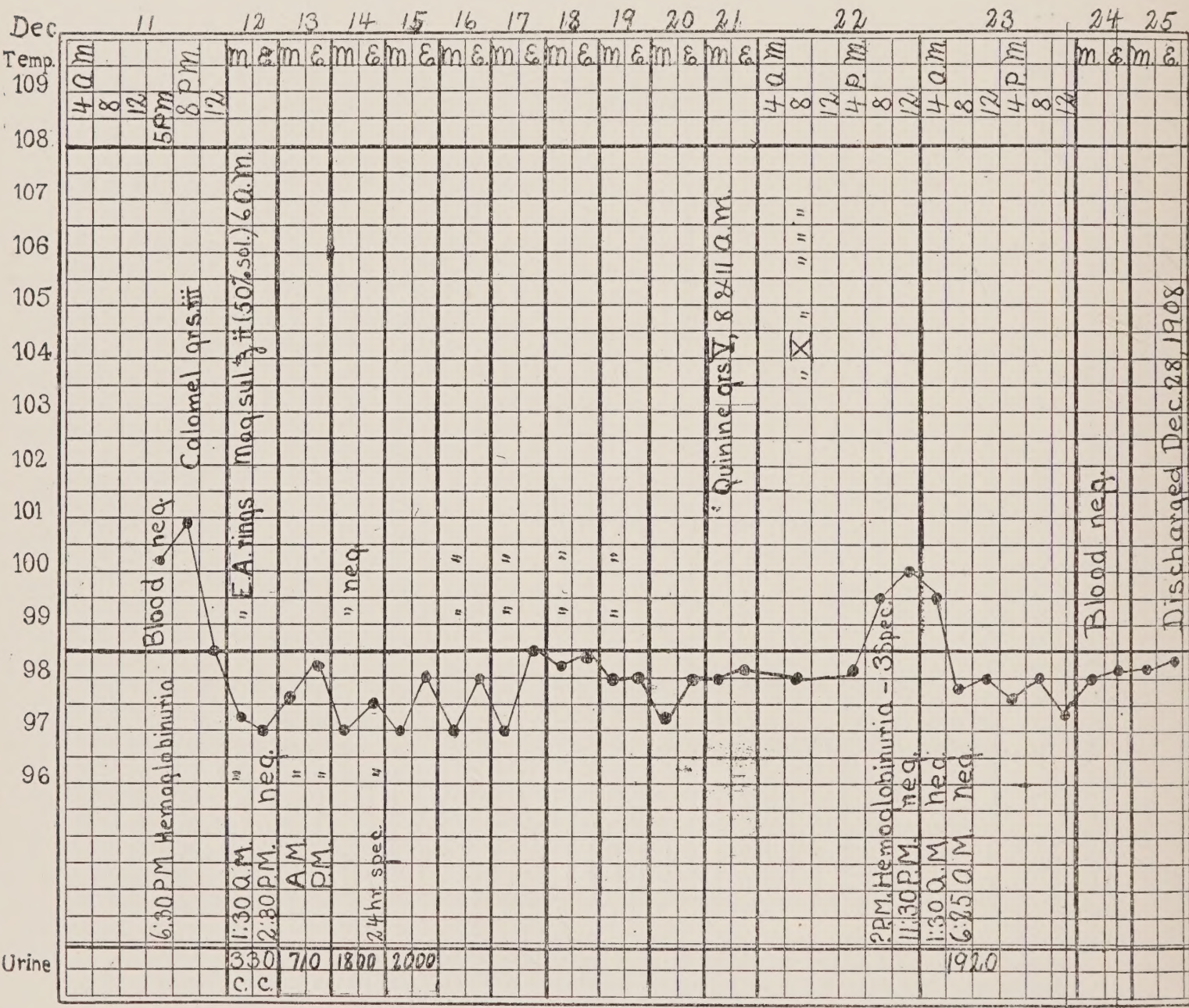


Chart 6.—No. 16,605. Patient, white, Austrian, who had been on the Isthmus one year, was admitted to Colon hospital, Dec. 11, 1908. The patient had had three previous attacks of "blackwater," had been sick two days, and had taken a quinin tablet every day for past ten days. On the morning of Dec. 11 the patient took 15 grains of quinin and at 4 p. m. noticed "blackwater." There was hemoglobinuria on admission. Estivo-autumnal (E. A.) parasites were found on second day. Quinin, grains x, were given on December 21 and grains xx on December 22. A transient hemoglobinuria followed.

April, 1910, 162 cases, and Colon Hospital from November, 1907, to May, 1910, fifty-nine cases—a total of 221 cases. For certain reasons all of the records of Colon Hospital prior to November, 1907, and many of the records of Ancon Hospital were not accepted and the cases excluded. There were eighteen recurrences in the hospitals among the 221 cases, and these have been considered separate attacks, since it sometimes happened that an initial attack was treated by one method while the recurrence was treated by another. The recurrences were considered separate attacks only when a period of not less than two days of hemoglobin-free urine intervened between attacks. There were, then, 239 attacks of blackwater represented by the 221 cases. These 221 cases include twenty cases previously reported by Gorgas,⁴ which in turn included fourteen cases reported by me.² They include, also, Herrick's nine cases referred to in my report.⁵

The 221 cases have been divided into two series, the first of which includes cases directly or indirectly under my care, the second all other cases.

Series 1.—My cases, seventy-three patients, eighty-four attacks. (Hemoglobinuria verified in almost every attack by the demonstration of hemin crystals or by the guaiac and turpentine test.)

Series 2.—Other cases, 148 patients, 155 attacks. (Hemoglobinuria often verified by above tests and diagnosis often made from appearance of urine with a heavy transient albuminuria.)

GENERAL TREATMENT

The most important general measure is the introduction of fluids by mouth, by rectum, subcutaneously or intravenously. The passage of a large quantity of urine is of the utmost importance, for the gravity of the prognosis increases with a decreased urinary output, and the majority of patients who die have suppression of urine. Sweat baths and the various diuretics may be tried, but I think that little is to be expected from them, and there is always a possibility of drug irritation of the affected kidneys. In a large number of the cases of Series 2, however, Basham's mixture was used as a routine procedure, and there appears to have been no injury done by it, although no good either. The bowels should be opened with calomel (3 to 5 grains is sufficient) followed by a saline cathartic; or, if vomiting prevents, enemas may be used.

The diet should consist of nourishing liquids, and during convalescence the patient's appetite may be the guide.

4. Gorgas, W. C.: *Malaria in the Tropics*, Jour. Am. Med. Assn., 1906, xlvii, 1417.

5. In order that no confusion may arise in future leading to repeated reports for mortality statistics of the same cases, a list of the hospital numbers of the cases included in this report is appended.

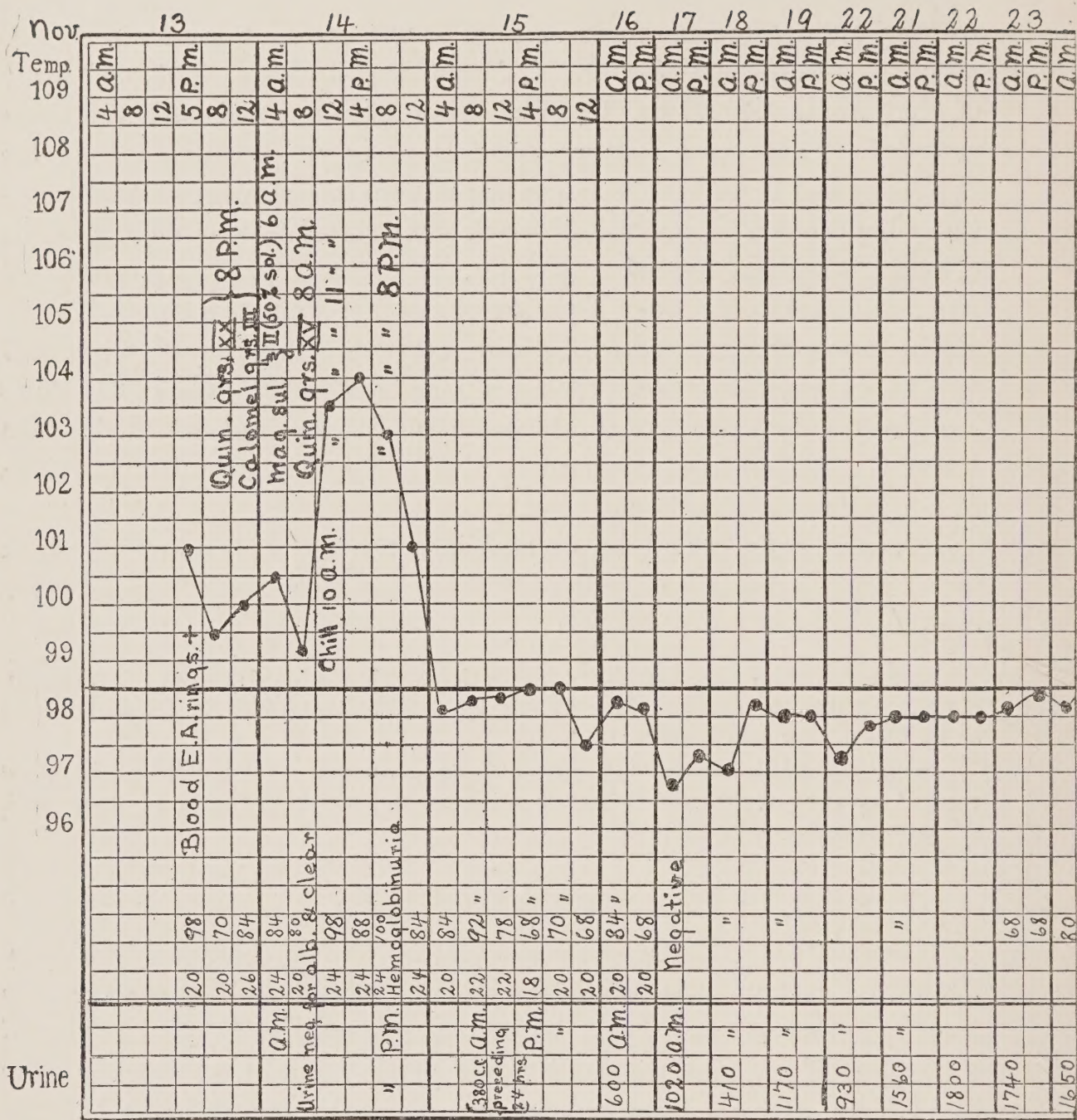


Chart 7.—No. 16,141. Patient, white, Spaniard, who had been in Panama nineteen months, was admitted to Colon Hospital July 25, 1909. The patient had had six previous attacks of malaria, and had been sick one day with present illness. Both attacks of hemoglobinuria in the hospital were apparently precipitated by quinin. Estivo-autumnal parasites were found on six separate examinations. Quinin was discontinued when hemoglobinuria developed, but when death approached quinin was ordered to be given by intramuscular injection. Autopsy was made fifteen hours after death. No parasites were found in smears from the brain, spleen, bone-marrow and liver.

For vomiting and restlessness morphin in repeated small doses given hypodermically is harmless and by far the most useful and satisfactory remedy. Crushed ice, also, may be useful.

Strychnin is the most satisfactory stimulant in cardiac or respiratory depression.

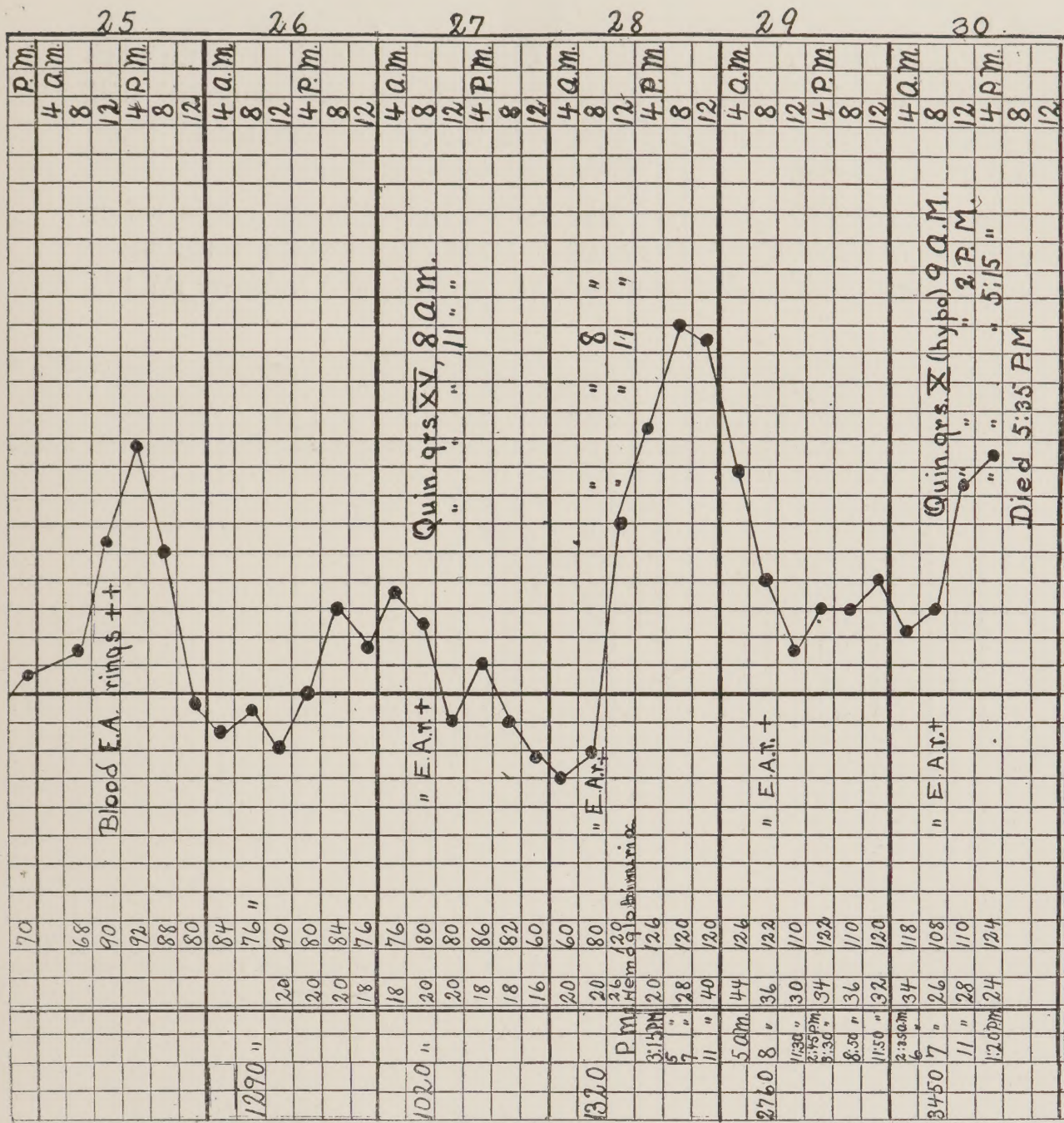


CHART 7—Continued

These general measures need little discussion, as they are ones on which all are practically agreed. I take it that the great question is still the one to be considered next.

QUININ TREATMENT

Relation of Quinin to Etiology.

Before one discusses whether or not it is wise to use quinin in the treatment of erythrolytic hemoglobinuria, it is meet that one's confession of faith be made regarding the relation that quinin bears to the onset of the disease. In Charts 2 to 11 inclusive, evidence that seems to be conclusive is presented in favor of the view that in certain cases, what-

ever may be the predisposing condition, quinin is the exciting cause. On the other hand, the recurrences in Charts 11, 12 and 13 furnish evidence that in other cases the onset may be in no way connected with the drug. The negative quinin history in the case represented by Chart 14 seems to be reliable. I have previously reported another attack occurring in an intelligent American who denied having taken quinin before the passage of blackwater.² The onset of many other attacks in this series was apparently associated with quinin (Chart 16), and in many the his-

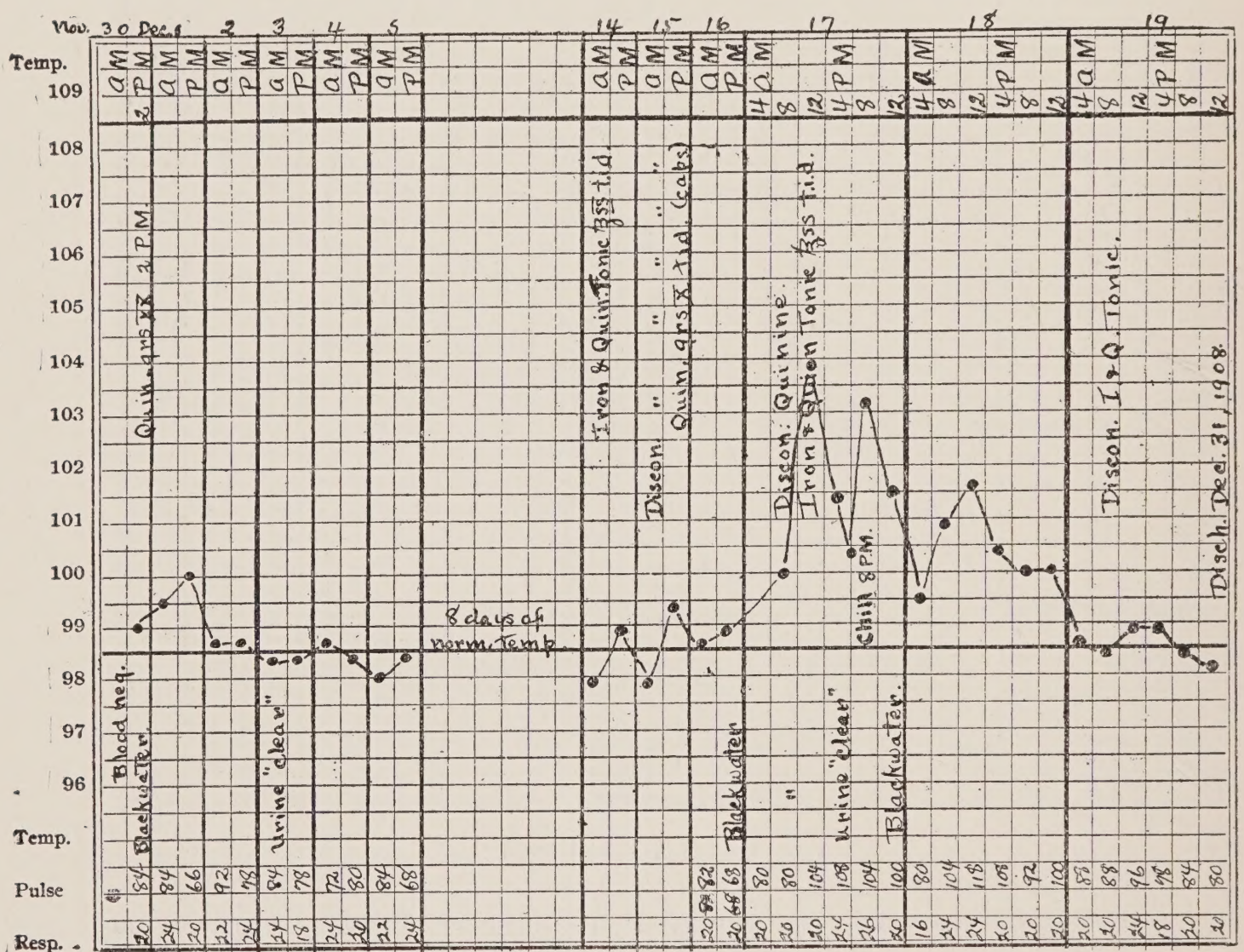


Chart 8.—No. 50,017. Patient, white, Spaniard, who had been on the Isthmus four and one-half months, was admitted to Ancon Hospital Nov. 30, 1908. The patient had been sick and passing "blackwater" five days before admission; had been jaundiced four days. "Blackwater" was present on admission. Recurrence followed iron and quinin tonic, which contained 15 grains of quinin in one ounce.

tory was indefinite or not solicited. The charts referred to represent the attacks most strikingly illustrating the truth in the views that quinin is and is not the exciting cause. That the number of striking instances of attacks precipitated by quinin is greater than the number arising without it is due, partly at least, to the fact that evidence in favor of the latter

view is more difficult to obtain. More or less fever usually precedes the onset of blackwater, and residents practically always take quinin on the slightest suggestion of fever. It follows, then, that nearly all patients who have hemoglobinuria in Panama have taken quinin before the onset, but it would be absurd to conclude that quinin precipitated the condition in every case or even in the majority of cases.

To sum up, I am sure that a few attacks of erythrolytic hemoglobinuria are precipitated by quinin, and also that a few develop without

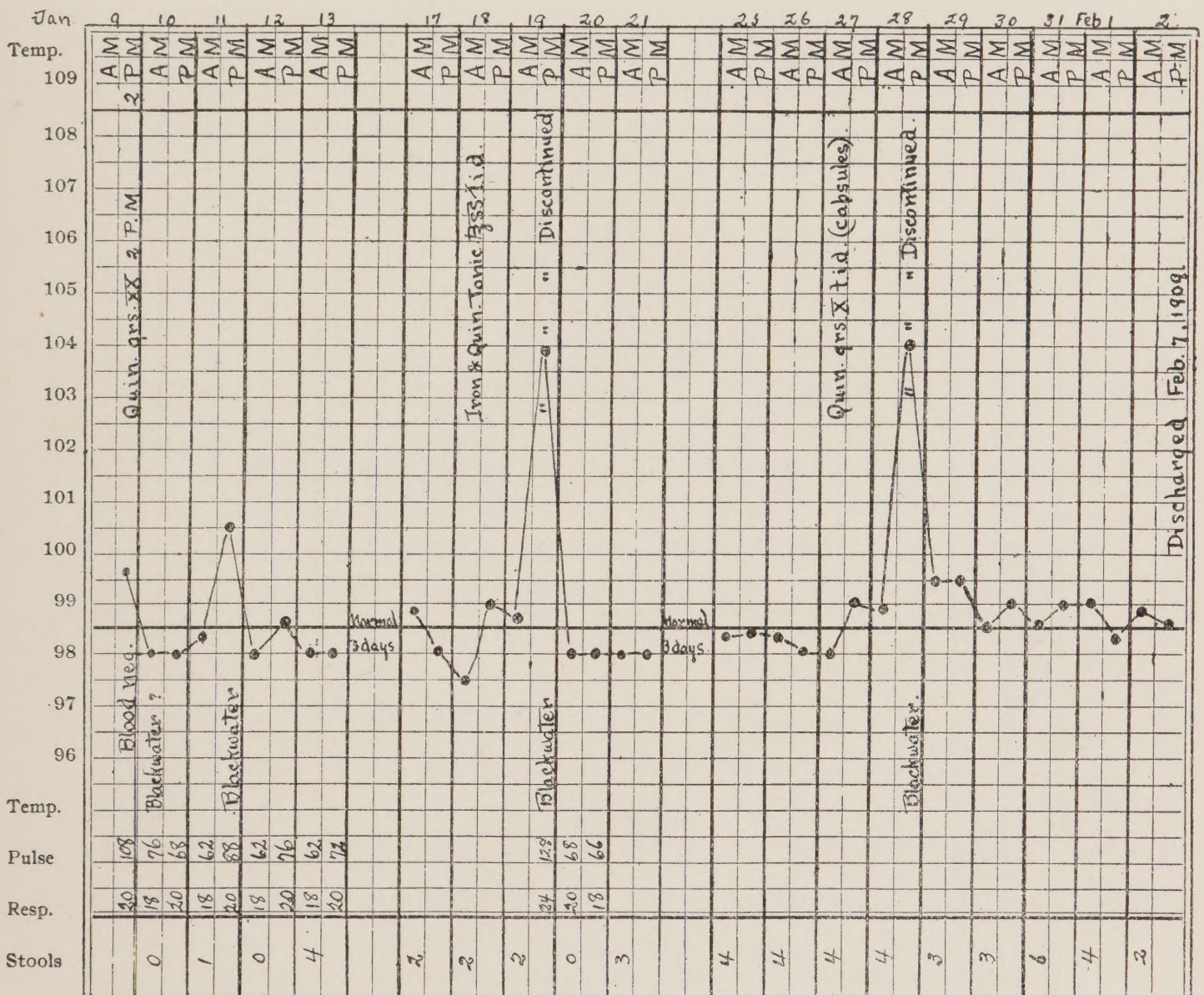


Chart 9.—No. 52,291. Patient, white, Jamaican, who had been on the Isthmus two years, was admitted to Ancon Hospital, Jan. 9, 1909. The patient had had "blackwater" on one previous admission to hospital. He had been sick three days and passed "blackwater" on day before second admission. Presence or absence of "blackwater" on admission was not stated in record. Iron and quinin tonic, 15 grains quinin to one ounce was given, and "blackwater" followed.

quinin, and good evidence is afforded that such is the case. I believe that a considerable number of the attacks that remain are precipitated by

quinin and that a larger number are not connected with the drug, but I cannot present evidence in proof.

Our knowledge, so far, of the part that quinin plays in the etiology of erythrolytic hemoglobinuria does not aid us greatly, therefore, in settling the question of its use in the treatment. Attacks that are precipitated by quinin (such as those represented by Charts 2 to 11) of course should not be treated with quinin. But these attacks cannot be definitely separated from others except in occasional recurrences that take place

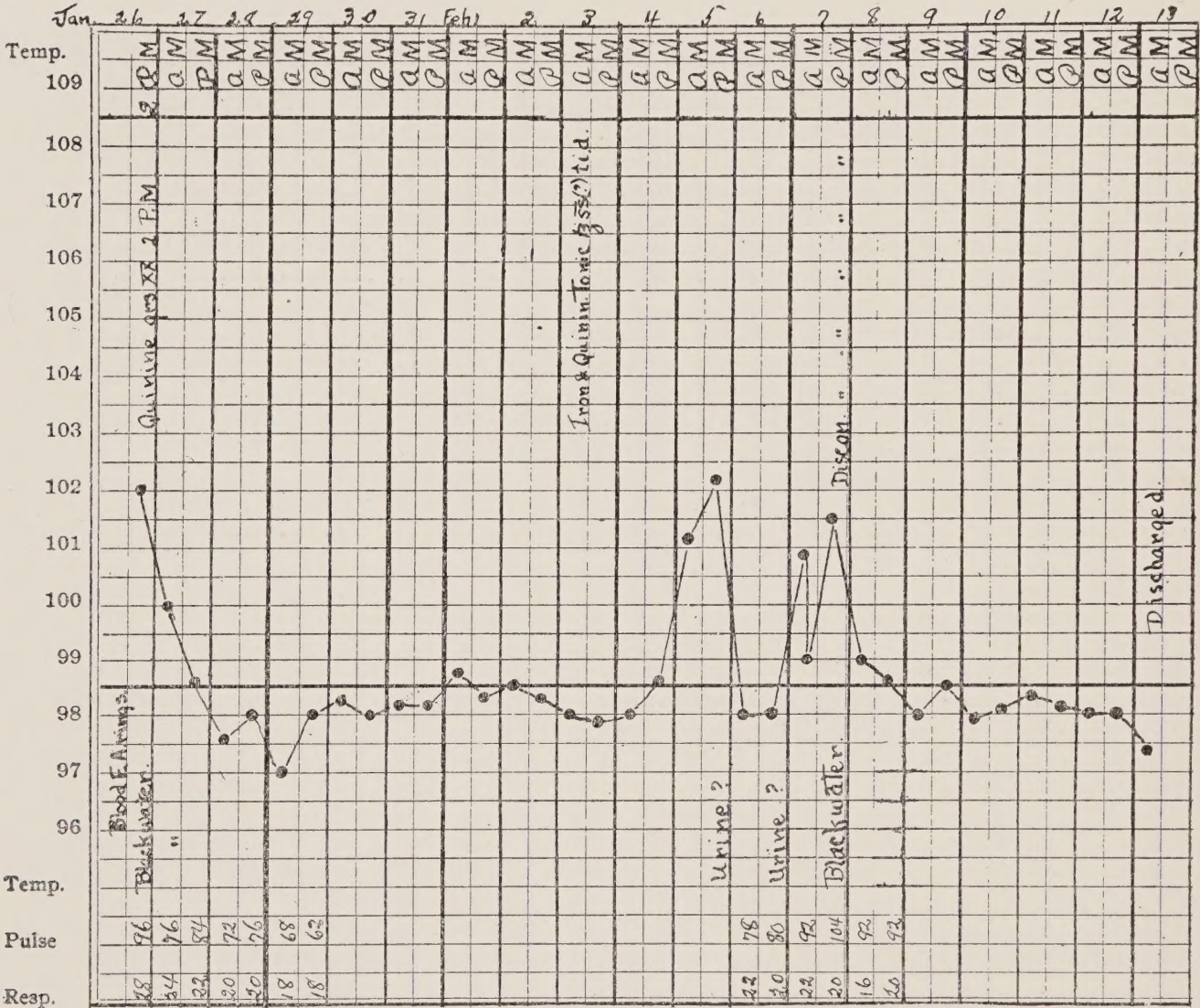


Chart 10.—No. 53,409 (Ancon). Patient, white, Italian, who had been on the Isthmus twenty-four months, was admitted to Ancon Hospital, Jan. 26, 1909. The patient had been previously admitted to hospital because of "blackwater"; had left hospital only nine days before second admission. He had been sick five days. The night before admission he passed "blackwater." Character of urine February 5 and 6 was not recorded, and the dose of iron and quinin tonic was not stated in record, probably half an ounce three times a day or quinin 7½ grains t. i. d.

while the patient is under observation and which follow promptly the administration of quinin after a period of apyrexia and hemoglobin-free urine.

One must turn to statistical studies and his own personal observations for guidance in a matter about which there is so much genuine difference of opinion.

Statistical Study

Deaderick's compilation of statistics in his recent book⁶ practically settles the matter in favor of treatment without quinin. The summary is as follows:

	Cases.	Deaths.	Mortality.
Treated with quinin.....	1821	472	25.9 %
Treated without quinin.....	1006	112	11.1 %
Treatment mixed or not recorded.....	3210	684	21.3 %

Deaderick thinks that "this number of cases probably eliminates all errors and should be convincing," in which opinion he is probably correct. My own statistics tend to confirm the above compilation, but the result is not nearly so striking. The difference may be partly a matter of interpretation, for I have found it not always an easy matter to classify a given case, and I have separated no class as having received mixed treatment, for the following reason. During the latter part of 1907 and the first eight months of 1908 we were treating all cases of blackwater fever with quinin in large quantities, usually by intramuscular injections. The treatment was never curtailed in severe cases, and all of the attacks could be placed frankly among those treated with quinin. In September, 1908, we began to treat a series of cases without quinin, and a certain number of them were of course severe and proceeded towards a fatal termination. It sometimes happened that the ward physician in immediate charge of such a case felt that nothing was being done for the patient, and the natural desire was that an attempt be made to do something, the courage required to watch the battle without interference failed, and the patient received quinin (Chart 7). It would certainly be misleading to take these fatal cases out of the class treated without quinin, for the mortality of this class would thereby be artificially lowered. I cannot but believe that this has happened to some extent in the statistics that Deaderick has done such able work in collecting. As for the mortality of the class treated with quinin, it is certain that in it have been placed all those cases of pernicious malaria in which hemoglobinuria was recognizable as "blackwater," and that these cases, belonging to the severest type of the disease, have very much increased the mortality of the class. After all is said, however, the difference is so great that one would be, perhaps, ultra-critical not to accept the general indication of the statistics in favor of withholding quinin in erythrolytic hemoglobinuria.

An attempt has been made in analyzing the cases of this report to avoid errors like those indicated above, and the cases have been placed

6. Deaderick: *Practical Study of Malaria*, W. B. Saunders Co., Philadelphia, 1909, p. 299.

in the class to which they belonged when the course was downward and the prognosis became grave. This was sometimes a difficult question to decide, but in the main I think that the result is trustworthy.

TABLE 1.—RESULT OF TREATMENT WITH AND WITHOUT QUININ

SERIES I: WRITER'S CASES, SEVENTY-THREE PATIENTS, EIGHTY-FOUR ATTACKS

Treated with quinin—	Attacks.	Deaths.	Mortality.
Whites.....	31	4	12.9 %
Blacks.....	10	4	40. %
Total.....	41	8	19.5 %
Treated without quinin—			
Whites.....	28	5	17.8 %
Blacks.....	15	2	13.3 %
Total.....	43	7	16.3 %

SERIES II: OTHER CASES, ONE HUNDRED FORTY-EIGHT PATIENTS, ONE HUNDRED FIFTY-FIVE ATTACKS

Treated with quinin—	Attacks.	Deaths.	Mortality.
Whites.....	36	5	13.9 %
Blacks.....	18	5	27.8 %
Total.....	54	10	18.5 %
Treated without quinin—			
Whites.....	83	12	14.5 %
Blacks.....	18	3	16.6 %
Total.....	101	15	14.8 %

SERIES I AND II: TWO HUNDRED TWENTY-ONE PATIENTS, TWO HUNDRED THIRTY-NINE ATTACKS

Treated with quinin—	Attacks.	Deaths.	Mortality.
Whites.....	67	9	13.4 %
Blacks.....	28	9	32.1 %
Total.....	95	18	18.9 %
Treated without quinin—			
Whites.....	111	17	15.3 %
Blacks.....	33	5	15.2 %
Total.....	144	22	15.3 %

The mortality of the white patients of each series and of the combined series shows a difference, under the two methods of treatment, so small that one death credited to the group of quinin-treated cases would even up the percentages. This difference is within the limits of error in classification. The mortality of colored patients treated without quinin is almost exactly equal to that of white⁷ patients, while of those treated with quinin more than double the percentage died. As far as the statistics go, therefore, they appear to indicate that in regard to life it makes little difference whether or not white patients receive quinin, while from colored patients it should be withheld.

Personal Observations

In a former communication² I concluded that quinin was strongly indicated in "malarial hemoglobinuria," that it should be given in large doses, and that properly given it appeared to be almost a specific. I beg

7. The kidneys of blacks appear to be much more susceptible to injurious influences than the kidneys of whites.

leave here to abandon that view, which I consider now to be erroneous. In spite of the fact that my mortality statistics present only qualified support of the antiquinin view, observation of a fair number of cases treated by both methods has convinced me that quinin does no good in any case of erythrolytic hemoglobinuria, and that in many it is emphatically injurious. With it the patients usually suffer more, the disease is more frequently severe, and in many instances the fever and the passage of blackwater are prolonged in a manner that one rarely sees when quinin is withheld (Chart 16). Weight is added to this view by the cases cited in which quinin certainly precipitated the attack, and by the less striking evidence that there are numbers of other instances in which the drug was probably responsible for the onset. In a number of cases, also, hemoglobinuria persisted while quinin was being given, but promptly ceased when it was withheld (Chart 15).

TABLE 2.—RESULT OF TREATMENT WITH AND WITHOUT QUININ IN BOTH THE PRESENCE AND ABSENCE OF MALARIAL PARASITES

	PARASITES PRESENT						PARASITES ABSENT					
	Quinin+			Quinin—			Quinin+			Quinin—		
	No. attacks.	No. deaths.	Mortality per cent.	No. attacks.	No. deaths.	Mortality per cent.	No. attacks.	No. deaths.	Mortality per cent.	No. attacks.	No. deaths.	Mortality per cent.
Whites (Series 1).....	7	1	14.3	15	3	20	24	3	12.5	13	2	15.4
Whites (Series 2).....	18	4	22.2	31	4	12.9	18	1	5.6	52	8	15.4
Total (Series 1 and 2) ..	25	5	20.0	46	7	15.2	42	4	9.5	65	10	15.4
Blacks (Series 1).....	3	1	33.3	7	1	14.3	7	3	42.9	8	1	12.5
Blacks (Series 2).....	9	1	11.1	3	1	33.3	9	4	44.4	15	2	13.3
Total (Series 1 and 2) ..	12	2	16.7	10	2	20.0	16	7	43.7	23	3	13.0
Whites and blacks												
(Series 1).....	10	2	20.0	22	4	18.2	31	6	19.4	21	3	14.3
Whites and blacks												
(Series 2).....	27	5	18.5	34	5	14.7	27	5	18.5	67	10	14.9
Total (Series 1 and 2) ..	37	7	19.0	56	9	16.1	58	11	19.0	88	13	14.8

Relation of Malarial Parasites to Quinin Therapy

Writers on blackwater fever have usually divided the cases into two groups according to the presence or absence of malarial parasites in the peripheral blood, and have recommended that quinin be employed in treating the first group and withheld from the second. Deaderick⁸ and Stephens⁹ are exceptions to this rule. It is Deaderick's opinion that "the only conditions in which quinin is indicated are, first, where the parasites show no tendency to disappear after forty-eight hours from onset; second, in the infrequent cases of intermittent hemoglobinuria where the outbreak corresponds with parasitic sporulation." Stephens goes a little

8. Deaderick: Practical Study of Malaria, p. 383.

9. Stephens: Osler's Modern Medicine, i, 458.

further and says, "if parasites still persist with a continuance of the fever then the question must be carefully weighed...If it can be avoided we should say it is better to abstain." Deaderick was unable to divide the cases of which he collected reports into groups according to the presence or absence of parasites. The attacks of the present report, however, can be grouped in such a manner and they bear on this point.

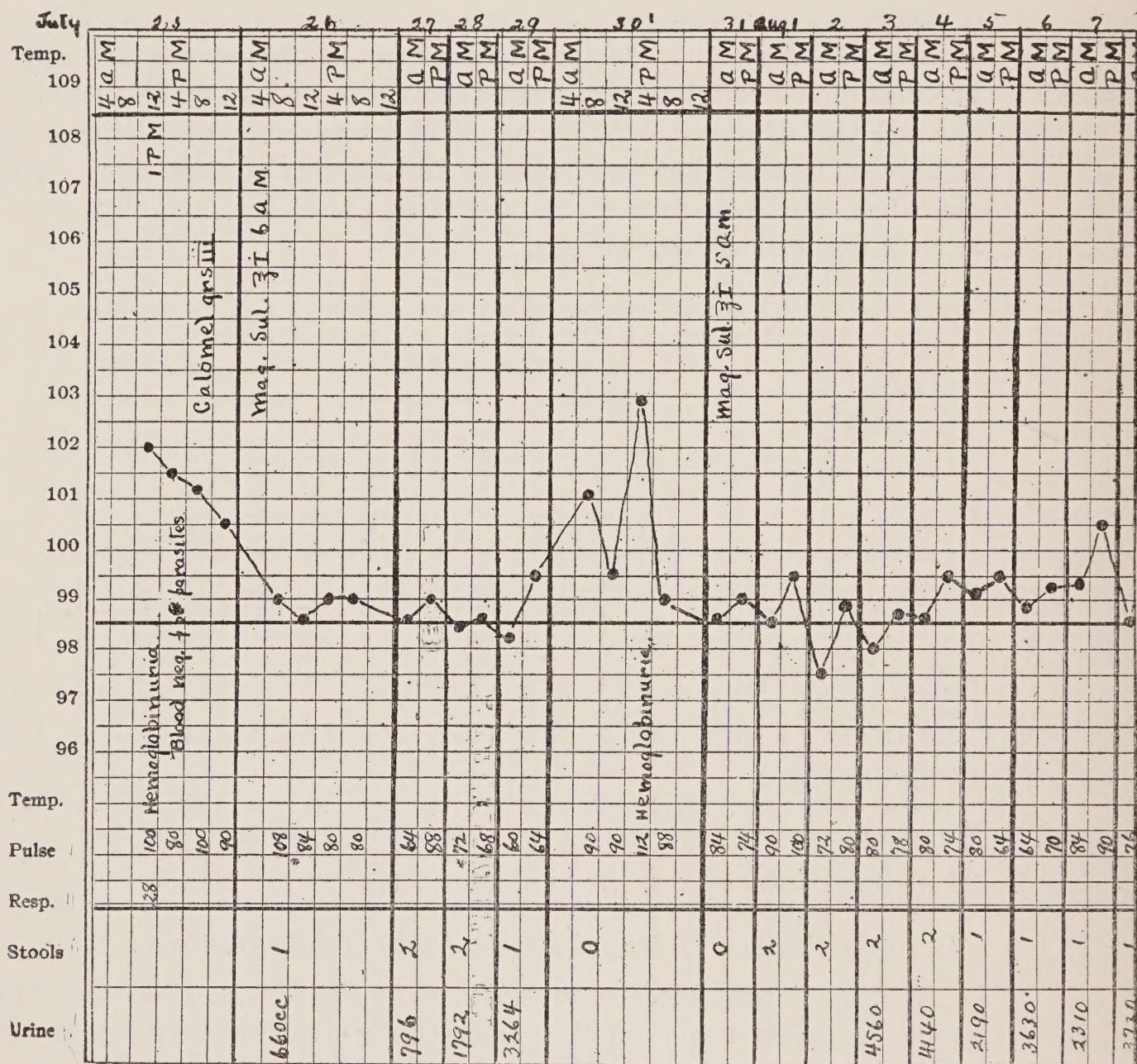


Chart 11.—No. 19,162. Patient, white, Spaniard, who had been on the Isthmus nineteen months, was admitted to Colon Hospital July 25, 1909. The patient had had malaria eight times previously, and before admission had been sick three days; had taken quinin and on the second day had passed "blackwater." He had been taking 9 grains of quinin daily before onset of the present illness. There were two recurrences; one arose spontaneously and one after taking quinin.

The whites of the "parasites present" group show a considerably higher mortality with quinin treatment than without it; the whites of the "parasites absent" group show a higher mortality without quinin than

with it. The mortality among the blacks occurs somewhat more according to expectation. The mortality of the combined whites and blacks of both groups is slightly smaller in the attacks treated without quinin. Therefore the presence or absence of malarial parasites appears to make no difference in the mortality. Nor have I been able to detect any difference in the clinical courses of members of the two groups.

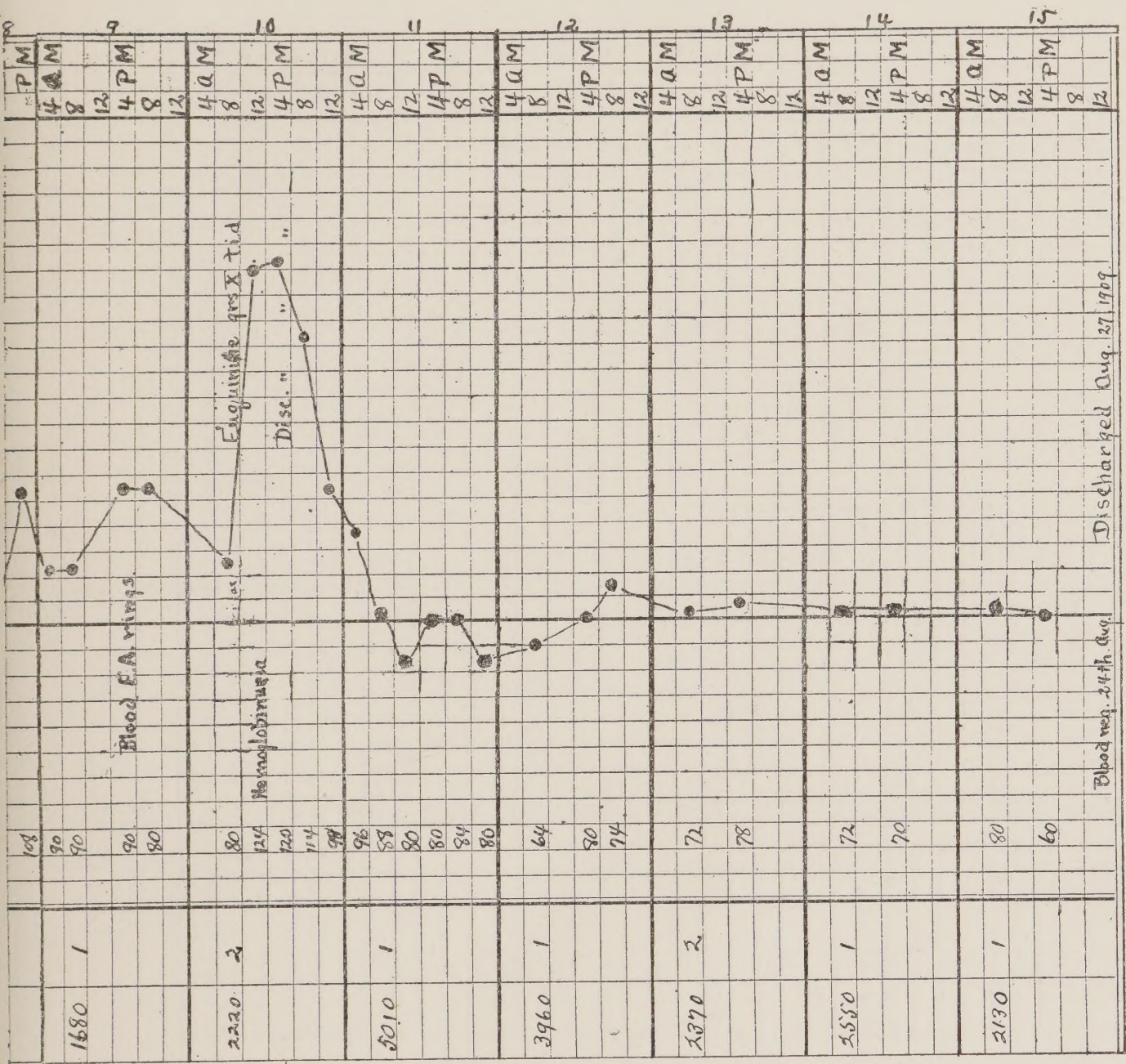


CHART 11—Continued

It is my opinion, therefore, that Deaderick and Stephens are quite right, as far as they go, in advising the withholding of quinin in most cases of blackwater fever, even if parasites be present in the blood. I should go a little further, however, and say that quinin should never be given during the passage of blackwater in cases belonging frankly to the

erythrolytic type of hemoglobinuria. If parasites persist in or return to the peripheral blood during convalescence, as frequently happens, or if a malarial type of fever recurs, quinin may be given with caution, beginning with small doses and gradually increasing. It may be fatal to begin at once with large doses of quinin (See Chart 7).

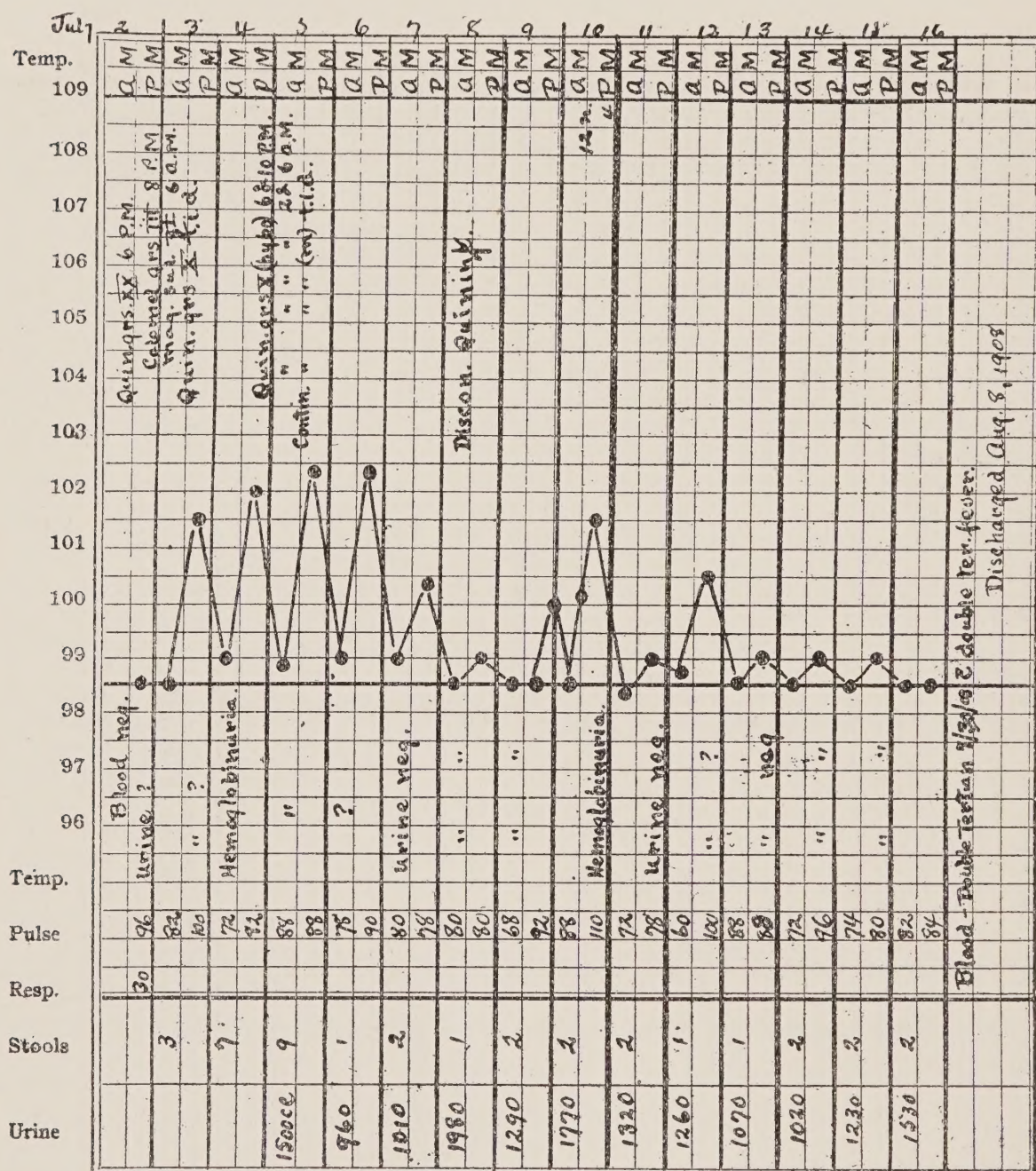


Chart 12.—No. 12,145. Patient, white, Spaniard, who had been on the Isthmus six months, was admitted to Colon Hospital July 2, 1908. The patient had had no previous malaria (?)—the present being the first time in hospital—and had never passed black urine. The patient had been sick four days and had taken quinin in solution twice daily since onset. The urine was “highly colored,” but not black. It is not certain from the record whether or not the patient had “blackwater” on admission. It apparently developed on the third day in the hospital. There was a recurrence three or four days after hemoglobinuria had ceased and two days after quinin had been discontinued. The double tertian infection possibly occurred in the ward. Quinin was given, 10 grains, t. i. d., and “blackwater” did not develop.

Serum Therapy

It would scarcely be proper to close without referring to the work of Christophers and Bentley¹⁰ and their suggestion that a serum therapy, such as that used in paroxysmal hemoglobinuria, is possibly in sight. Their work on iso-agglutinins and isohemolysins and their conclusions¹¹

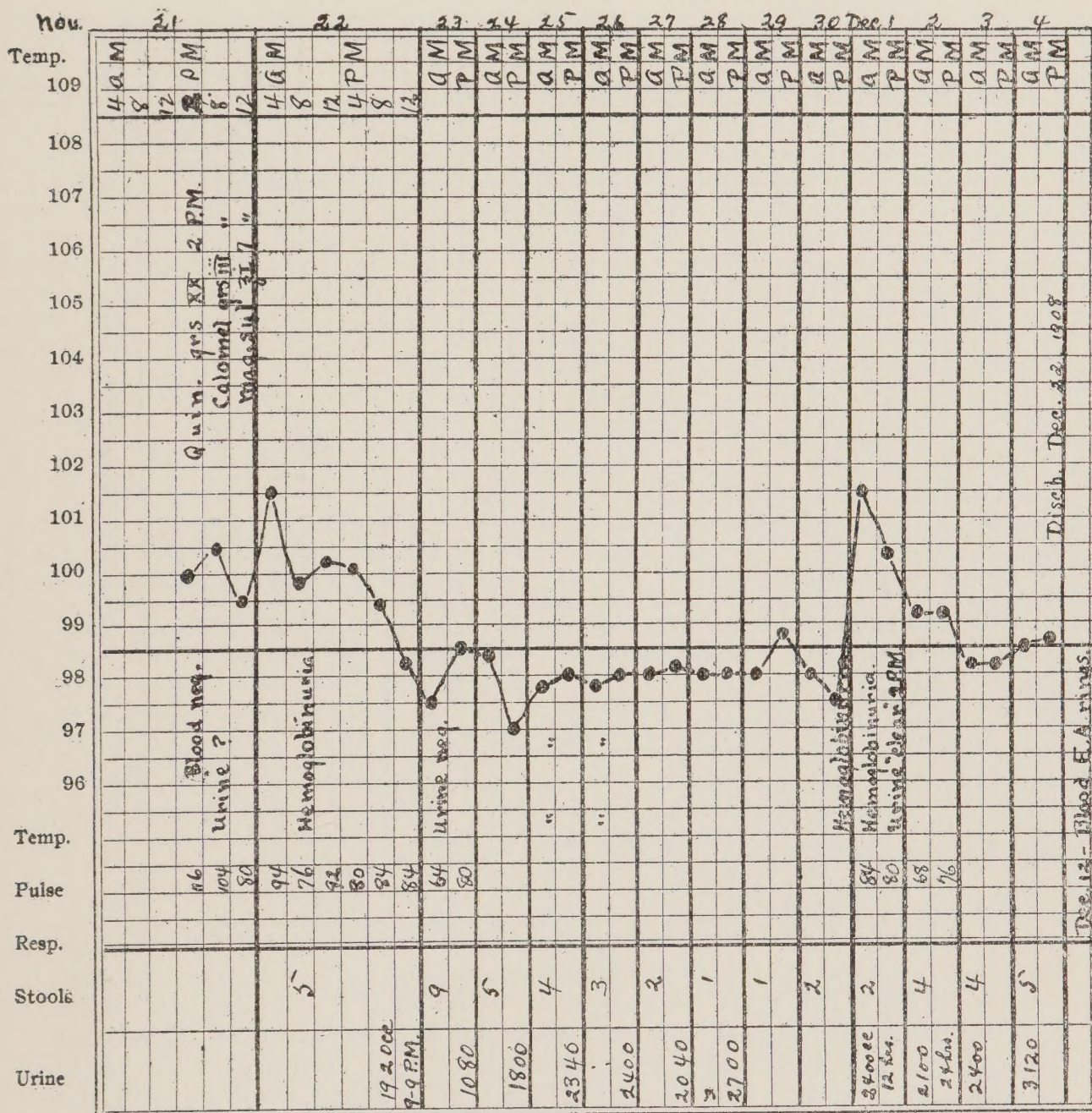
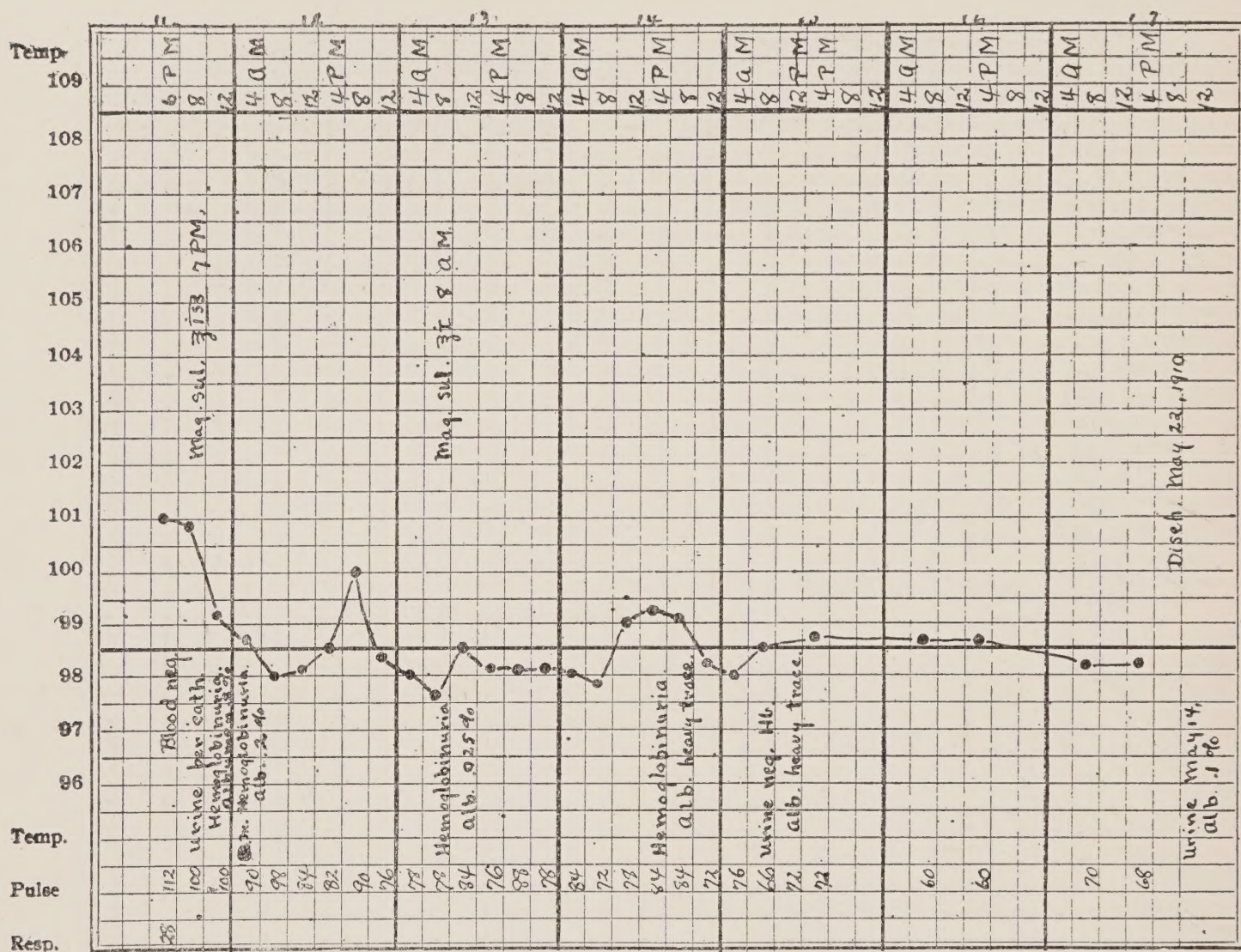


Chart 13.—No. 49,539. Patient, white, Portuguese, who had been on the Isthmus fifteen months and in hospital four times, was admitted to Ancon Hospital Nov. 21, 1908. The patient had been sick three days, passing "blackwater" two days. There was spontaneous recurrence of hemoglobinuria. Fever recurred on Dec. 12 and estivo-autumnal organisms were found. The patient was given 30 grains of quin in daily without recurrence of "blackwater."

10. Christophers and Bentley: Blackwater Fever, Scient. Mem. Gov. India. (new series), 1908, No. 35, pp. 181, 182.

11. Christophers and Bentley: Blackwater Fever, Scient. Mem. Gov. India. (new series), 1908, No. 35, pp. 154-179.

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but in the beginning I met results which were incapable of explanation by their hypotheses, and which were explained only when Moss' paper appeared. Moss was able to classify all human bloods into four groups according to the agglutinating reactions of serums and corpuscles. With this classification as a working basis, we shall be able now to approach the study of the blood in erythrolytic hemoglobinuria with a degree of comprehension hitherto not possessed.

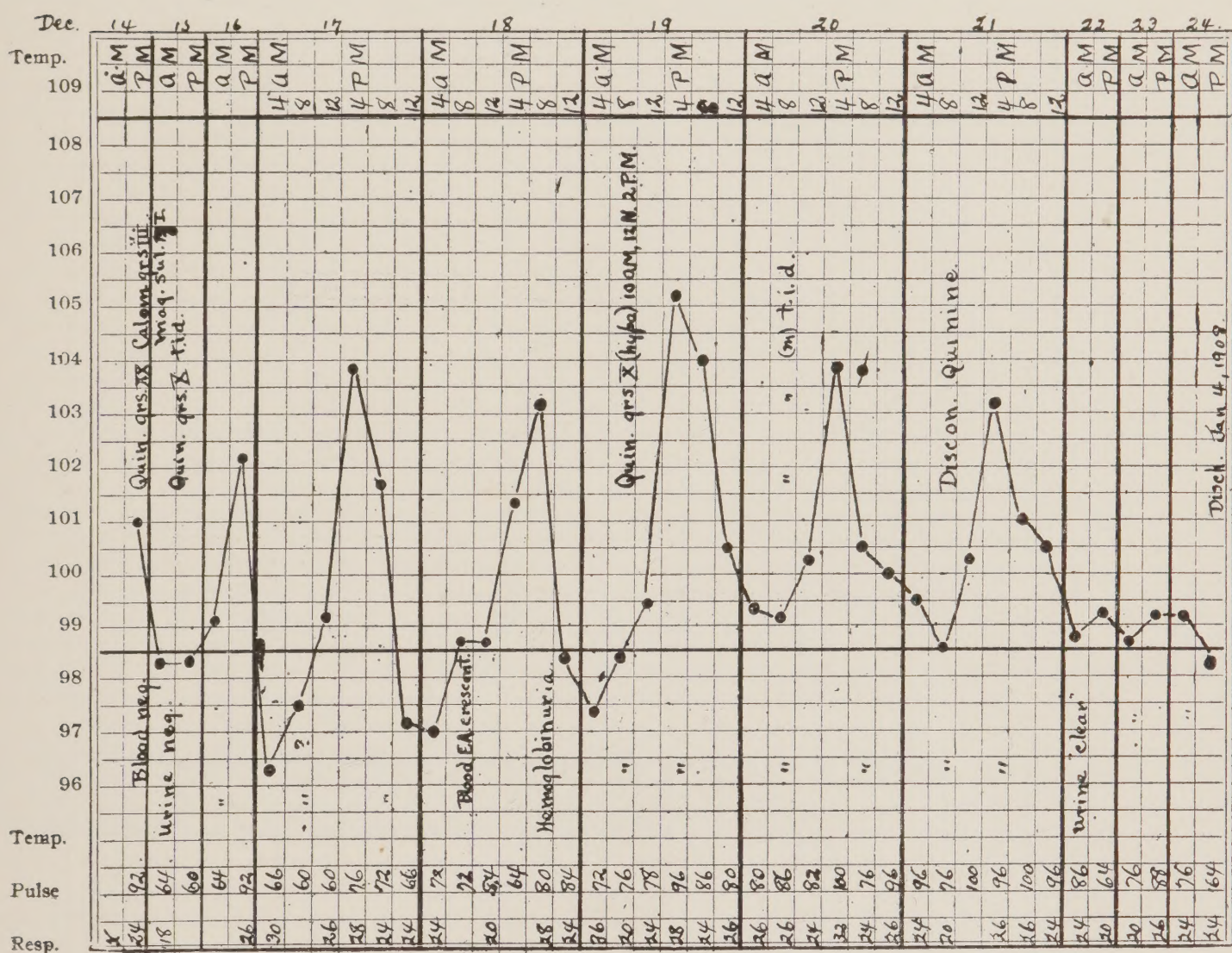


Chart 15.—No. 8,877. Patient, colored man, Jamaican, who had been on the Isthmus three years, was admitted to Colon Hospital Dec. 14, 1907. The patient had "blackwater" fever in Jamaica, 1903; no quinin had been given previous to onset; patient treated with quinin and "blackwater" lasted six days. "Blackwater" fever again occurred on the Isthmus, March, 1907, but the patient did not remember whether or not he took quinin before onset; he was then treated with quinin by intramuscular injection, and "blackwater" continued five days. On present admission no "blackwater," which was apparently precipitated by quinin and continued until quinin was discontinued. Patient's brother was in hospital at same time with "blackwater," apparently precipitated by quinin (Chart 4).

SUMMARY

1. Blackwater fever is a term that includes two types of hemoglobinuria more or less definitely associated with malaria. It is important

that the two types be separated for study and treatment. The indications for treatment are diametrically opposed. The two types probably differ in the mechanism of their production and their clinical phenomena are different.

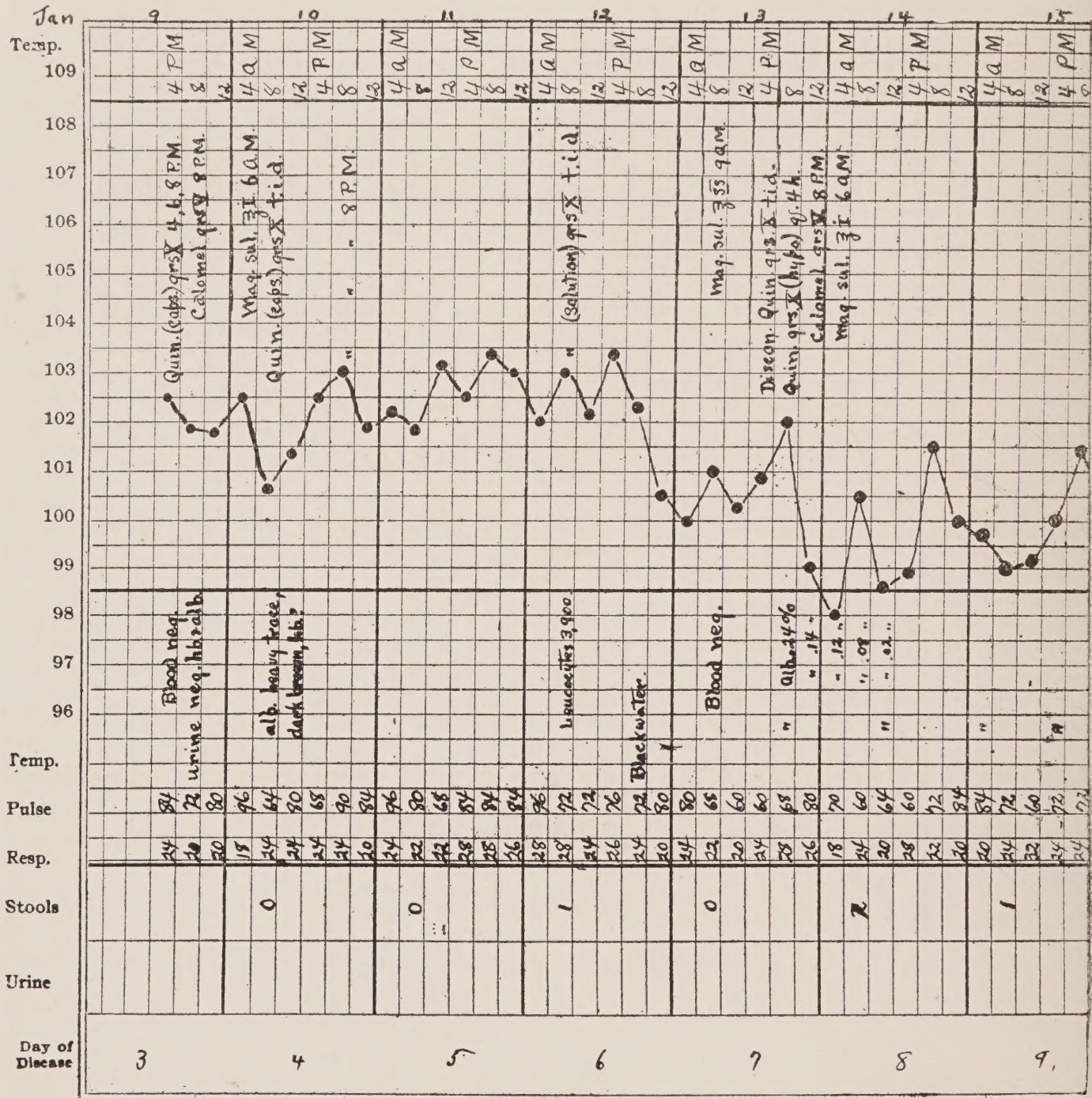
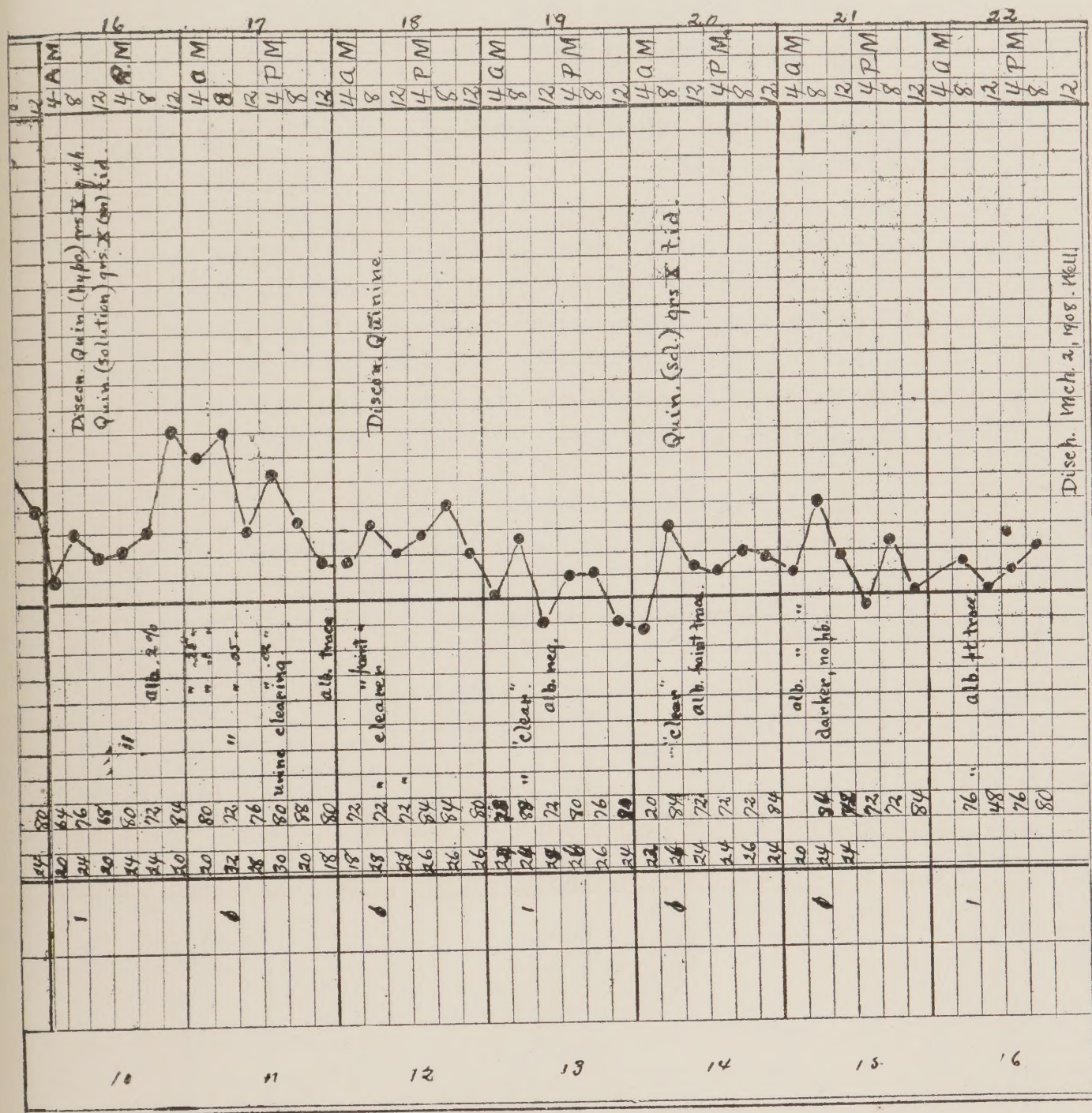


Chart 16.—No. 9,322. Patient, white, Australian, who had been on the Isthmus over three years, was admitted to Colon Hospital, Jan. 9, 1908. The patient had had fever three times previously. "Blackwater" fever occurred three years ago on the Isthmus. Onset occurred Jan. 7, 1908, with chill and fever; January 8, chill fever and "blackwater." Quinin history was not recorded. There was no "blackwater" on admission, but continued fever, possibly "post-hemoglobinuric." Quinin in solution was given on January 12 and hemoglobinuria developed that night. The patient was treated vigorously with quinin. Prolonged, severe course followed. The hemoglobin fell to 30 per cent. January 18. Widal test was negative January 18 and 22.

2. Type 1.—Hemoglobinuria associated with pernicious malarial infections. The hemoglobinuria is probably brought about by immediate destruction of erythrocytes by enormous numbers of sporulating parasites, and the time of its appearance can generally be foretold with a



fair degree of accuracy. The treatment is that of pernicious malarial fever. Type 2.—Hemoglobinuria indefinitely associated with malaria and probably brought about by the solution of erythrocytes by an unknown hemolysin.

3. It is proposed that the terms "blackwater fever," "malarial hemoglobinuria," "hemoglobinuric fever," etc., be abandoned and that the two types of hemoglobinuria hitherto embraced by them be known as follows:

Type 1.—Pernicious malarial fever with hemoglobinuria.

Type 2.—Erythrolytic hemoglobinuria.

4. A number of attacks of erythrolytic hemoglobinuria in this series of cases were precipitated by quinin, a large number of attacks were apparently precipitated by quinin, and a few recurrent attacks developed in the wards when no quinin had been given.

5. Statistical studies of 239 attacks of erythrolytic hemoglobinuria, supplemented by personal observation indicate that quinin should never be given during hemoglobinuria.

6. The presence of malarial parasites in the blood of patients with erythrolytic hemoglobinuria has no effect on the mortality or on the clinical phenomena, and affords no indication for treatment during hemoglobinuria. When parasites persist or reappear during convalescence or when fever persists or recurs after the cessation of hemoglobinuria, quinin should be given guardedly. The dose should be small at first and gradually increased, if hemoglobinuria is not precipitated.

REPORT OF CASES¹³

CASE 1 (Chart 1).—Pernicious malarial fever with hemoglobinuria, No. 23,811.

BLOOD EXAMINATIONS

Time.	Hemoglobin (Sahli hemom.).	R. B. C. per c.mm.	Color index	Number R. B. C. counted.	Number infected.	Percentage infected.
15— p. m.	..		..	500	78	15.6
16— 9:00 a. m.	..		..	500	47	9.4
16—10:00 a. m.	85		..		..	
16—11:30 a. m.	..		..	500	27	5.4
16— 4:00 p. m.	..		..	500	23	4.6
16— 4:30 p. m.	85	4,760,000	.89		..	
16— 7:00 p. m.	..		..	500	18	3.6
16—12:00 m.	..		..	500	9	1.8
17— 4:00 a. m.	..		..	3,500 (approx.)	20 fields*	16 .46
17— 8:30 a. m.	..		..	4,500 (approx.)	25 fields	6 .13
17— 9:30 a. m.	93	5,192,000	.9		..	
17— 4:00 p. m.	..		..	5,000 (approx.)	25 fields	5 .1
18— 8:00 a. m.	93	4,872,000	.95	50 fields	0	0
18— 3:00 p. m.	..		..	50 fields	0	0
19—10:00 a. m.	..		..	50 fields	0	0
19— 4:00 p. m.	91		..		..	
20— 1:30 p. m.	84	5,008,000†	.84		..	
25—10:00 a. m.	81		..		..	

13. Only Case 1 is discussed in detail. Synopses of the other cases (2-16) appear as legends under the respective charts.

* B. and L. objective 1/12 and ocular 1. Actual counts of the corpuscles in a number of fields in which the corpuscles were more and less thickly spread varied from 175 to 250 per field. The estimates were made from these standards, taking into consideration the thickness of the smear.

† 8:30 a. m.

URINE EXAMINATIONS

May.	Time.	Color.	Sp. Gr.	Reac.	Albumin.	Guaiac and Turpentine Test.	Sediment.	Microscopic Examination.
16—	1:20 a. m.	Brownish-red	1,028	Acid	Heavy trace (boiling)	Negative	Mucous cloud...	A few hyaline and hyalogramic casts; no r. b. c.
16—	1:30 p. m.	Brownish-yellow	1,033	Acid	Faint trace	Negative	None.....	A few hyaline and hyalogramic casts; no r. b. c.
16—	4:40 p. m.	Brownish-yellow	1,030	Acid	Trace	Suspicious	Pus Shred.....	A few hyaline and hyalogramic casts; no r. b. c. + pus cells
17—	5:30 a. m.	Blackwater, dark, cloudy, smoky, brownish-red by transmitted light	1,028	Alk.	Will not settle in Esbach tube; 25 per cent. wet	Intense reaction.....	Heavy, grayish-brown	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c.
17—	11:00 a. m.	Blackwater, yellowish-red, less intense	1,025	Acid	Heavy trace.....	Supernatant urine; 1-100 dil. is robin-blue; sediment is blue-black (1-100)	Heavy, greenish brown	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c.
17—	5:15 p. m.	Suggests black water, brownish-red, less intense	1,023	Acid	Heavy trace.....	Mixed urine; 1-10 dil. is violet-blue	Heavy, greenish brown (less)	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c.
17—	10:40 p. m.	Yellowish-red, not like blackwater			Trace	Supernatant urine; 1-10 is violet-blue	Mucous cloud...	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c. (few casts)
18—	4:45 a. m.	Yellowish-red, not like blackwater			Trace	Undiluted urine is violet-blue	Mucous cloud...	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c. (few casts)
18—	10:20 a. m.	Yellowish-red, not like blackwater		Acid	Faint trace.....	Undiluted urine is violet-blue	Mucous cloud...	Brown amorphous detritus; numerous hyalo-granular casts, covered with brown material; no r. b. c. (few casts)
18—	4:30 p. m.	Yellowish-red, not like blackwater		Acid	Very faint.....	Supernatant urine is negative; sediment is violet-blue	Very slight.....	Very few hyaline and hyalogramic casts; no r. b. c.
19—	3:10 a. m.		1,023		Very faint.....	Supernatant urine is negative; sediment is violet-blue	Very slight.....	
19—	10:20 a. m.		1,022	...	Negative	Negative	Very slight.....	
19—	3:00 p. m.				Negative	Negative		
20—	8:00 a. m.				Negative	Negative		

Patient.—Colored man, Martiniquan, aged 30, laborer, admitted May 15, 1910, 4 p. m.

History.—The patient had been on the Isthmus thirty-one months, had had seven previous attacks of fever in Panama, and many in Martinique. During fever attacks he had never noticed that urine was black or red. He said that he had been sick three days with fever, vomiting and headache, and had not taken quinin before admission.

Examination.—The patient was very restless on admission, tossing from side to side in bed and complaining of great pain in his head. His mind seemed fairly clear. Examination of heart, lungs and abdomen was negative; the spleen was not palpable. The blood was found to contain enormous numbers of small ring forms of estivo-autumnal malarial parasites. The imminence of hemoglobinuria was suspected and every specimen of urine was ordered to be sent when voided to the laboratory.

Course of Illness.—On the following day, May 16, the patient was quiet, but seemed very ill and extremely prostrated. Leukocytes numbered 7,100. At 8 p. m. his temperature rose abruptly from normal to 102 F. There was no chill, but vomiting occurred. The next urine voided, at 5:30 a. m. May 17, had the characteristic appearance of "blackwater." The patient did not pass into coma, or even lose consciousness, but he appeared to be extremely ill and profoundly depressed. The sclerotics became slightly jaundiced, but the spleen never became palpable or enlarged to percussion. Hemoglobin could be detected in the urine in traces until 3:10 a. m., May 19. Improvement was rapid from May 18 onward.

DISCUSSION OF THE CASE

Blackwater was prognosticated from an examination of the blood. More than 15 per cent. of the red corpuscles in the peripheral blood were infected. The number infected in the internal organs was probably much larger. In spite of the enormous infection, hemoglobin estimations and erythrocyte counts indicated but slight blood destruction, and the results were in striking contrast to the blood-picture in erythrolytic hemoglobinuria, in which, even in mild cases, blood destruction, as indicated by the same methods, is terrific. (Other cases have confirmed the blood findings given above.) The increase of hemoglobin and erythrocytes on May 17 was probably due to concentration of blood from loss of fluid by vomiting and urination. It seems quite certain that quinin in this case not only killed parasites in the intracorpuseular stage, but also prevented the destruction of many infected corpuscles. The parasites themselves showed evidence of the influence of quinin by their vacuolated and often bizarre appearance. The urine did not differ from the ordinary "blackwater" urine.

In conclusion, I wish to thank Colonel Gorgas for permitting me the use of the above material, and for consenting to the publication of the paper.

HOSPITAL NUMBERS OF CASES INCLUDED IN ABOVE REPORT

ANCON HOSPITAL CASES, 162

98	12,506	23,573	49,146	53,646	58,252
400	653	719	303	681	413
535	13,445	831	317	696	637
542	459	25,282	419	806	59,622
1,401	463	304	446	54,016	664
1,469	879	362	539	202	776
2,065	14,369	575	50,017	292	61,930
2,721	15,093	26,308	980	341	63,139
3,060	938	31,457	51,364	394	274
4,263	945	32,205	607	500	364
4,266	16,525	34,115	753	956	564
4,515	979	125	758	55,111	696
6,418	17,018		969	104	64,680
6,970	18,109	36,162	971	189	65,036
7,110	363	249	52,192	218	66,592
8,408	489	534	206	348	828
8,823	981	38,349	291	468	966
9,004	19,329	711	386	56,137	976
9,372	20,304	735	454	550	68,273
9,925	158	47,423	479	717	703
10,107	222	525	496	729	757
10,163	231	605	53,031	969	759
10,474	433	637	52	57,473	703
11,627	21,975	781	55	617	873
11,991	22,428	788	139	731	69,290
12,271	762	48,075	409	58,065	516
					71,243
12,383	23,320	384	479	157	72,431

COLON HOSPITAL CASES, 59

8,711	9,971	12,645	15,347	16,655	17,837
8,877	10,021	875	372	687	978
9,036	77	13,069	735	758	18,199
130	126	81	742	879	19,162
300	344	102	16,141	957	20,231
322	590	449	295	17,307	21,301
370	964	817	402	471	425
516	967	965	520	488	645
842	12,055	14,272	602	548	23,174
950	145	15,213	605	734	



